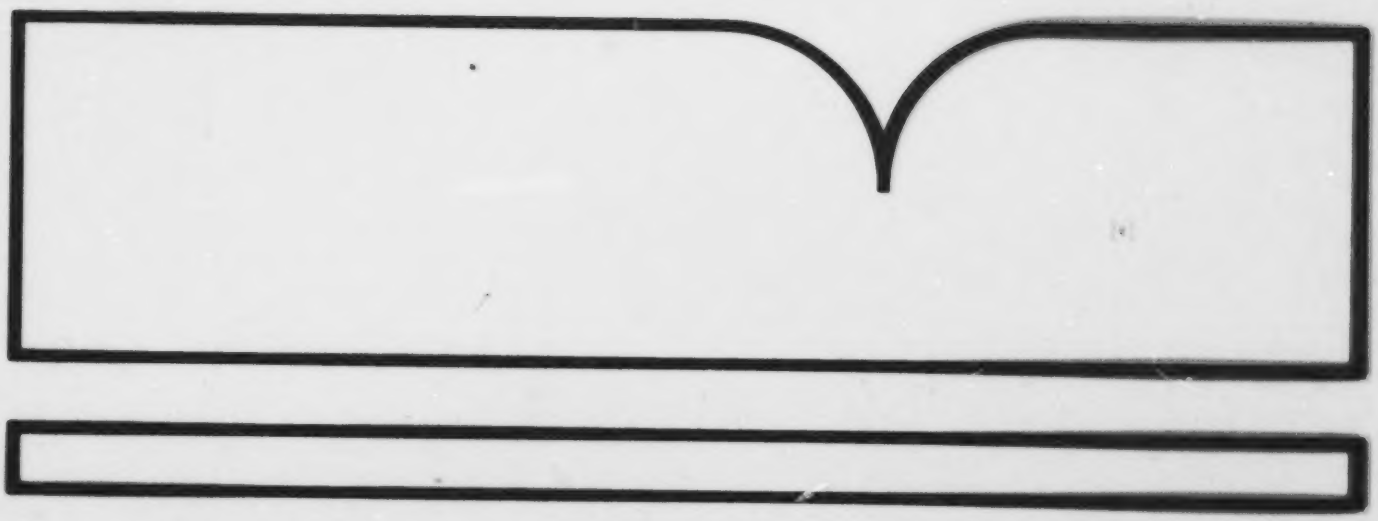
PB89-123376

Health and Environmental Effects Profile for Isobutanol

(U.S.) Environmental Protection Agency
Cincinnati, OH

May 86



U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/X-86/149	2.	3. RECIPIENT'S ACCESSION NO. PB89 123376/AS
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Isobutanol		5. REPORT DATE May 1986 6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

The Health and Environmental Effects Profile for Isobutanol was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Isobutanol has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for Isobutanol is 0.3 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for Isobutanol is 1000.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 69
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

EPA/600/X-86/149
May 1986

PB89-123376

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ISOBUTANOL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA. 22161

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3112. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

Isobutanol (CAS number 78-83-1) is a colorless liquid with a sweet musty odor. It is miscible with ethanol and ether, but is partially soluble in water (Verschueren, 1983; Rowe and McCollister, 1982). In 1984, five U.S. companies at seven locations manufactured isobutanol (SRI, 1985). About 163.15 million pounds of isobutanol were produced in the United States in 1984 (USITC, 1985) and in 1981, 14 million pounds were imported (TSCA-ITC, 1980). Isobutanol is made commercially as a by-product of the oxo process (SRI, 1985) and is used primarily as a solvent and intermediate (TSCA-ITC, 1980; Lawler, 1977; Windholz, 1983).

In ambient water, hydrolysis and oxidation of isobutanol by hydroxyl radicals are not expected to be important reaction processes. In activated sludge systems, isobutanol has been significantly biodegraded. Although no data on the biodegradability of isobutanol in natural waters are available, the results of biodegradation in activated sludge are used to indicate that significant biodegradation will occur in natural waters.

Volatilization of isobutanol may be significant in aquatic media (Lyman et al., 1982). The relatively low octanol/water partition coefficient (K_{ow}) and high water solubility (WS) suggest adsorption to sediments and bioconcentration in aquatic organisms are unlikely.

In the atmosphere, reactions with OH• radicals and NO_x are likely to be the significant fate processes for isobutanol. Its half-life resulting from OH• reaction is expected to be ~1 day. Removal of atmospheric isobutanol through dry deposition and adsorption onto particulate matters and subsequent deposition are likely to be insignificant. Because of its reasonably high WS, wet deposition may be somewhat significant in removing atmospheric isobutanol.

Based on its behavior in aquatic media, both volatilization and biodegradation processes are expected to play important roles in the loss of isobutanol from soil. The estimated K_{oc} data also indicate that isobutanol should be highly mobile in soil. If the biodegradation of isobutanol in soil becomes less competitive compared with its leachability in soil, substantial leaching of the compound into groundwater will occur.

The general population is almost continuously exposed to low levels of "natural" isobutanol (U.S. EPA, 1983), which is produced by the fermentation of carbohydrates (Windholz, 1983). Thus, isobutanol can enter air, water and food from a variety of sources; however, considerably higher concentrations of isobutanol are expected to evolve from sites where isobutanol is produced, processed or used, rather than from nature (U.S. EPA, 1983). Isobutanol has been monitored in river water and one groundwater sampling area (Yasuhara et al., 1981; Botta et al., 1984). Several sources of emissions into air have been reported, including volatilization from palm mill effluent (Hwang et al., 1978), petrochemical processes and storage, solvent use and animal wastes (Graedel, 1978; Yasuhara et al., 1984).

Isobutanol has been found in various edible items including some fruit (SRC, 1980), fried chicken (Tang et al., 1983) and most alcoholic beverages (TSCA-ITC, 1980).

Dermal exposure may result primarily from the use of products containing isobutanol as a solvent or during its direct use as a solvent (Luedersdorf et al., 1985; U.S. EPA, 1983).

Concentrations of isobutanol acutely toxic to the aquatic species studied are measured in g/ℓ, indicating that isobutanol is relatively nontoxic and not likely to cause ecological effects in the environment (TSCA-ITC, 1980). Sublethal effects have been reported at lower concentrations, the most sensitive of which was the threshold for cell multiplication

inhibition of the bacterium Pseudomonas putida at 280 mg/ℓ. The limited information available indicates that isobutanol is not highly toxic to aquatic organisms.

Isobutanol is readily absorbed through gastrointestinal and pulmonary mucosa (Browning, 1965; Saito, 1975; Bonte et al., 1981). It is metabolized to isobutyraldehyde, then to isobutyric acid, which may enter the tricarboxylic acid cycle by a Coenzyme A-mediated pathway (Saito, 1975). While Saito (1975) detected unchanged isobutanol, acetaldehyde, acetic acid, isobutyraldehyde and isovaleric acid in the urine of rabbits dosed orally with isobutanol, Kamil et al. (1953) failed to detect aldehydes in the urine or breath of orally dosed rabbits.

Kamil et al. (1953) administered ~618 mg/kg isobutanol by gavage to rabbits. After 24 hours, 4.4% of the dose was excreted as a glucuronic acid conjugate in the urine. Analysis of urinary or breath data suggested that a negligible fraction of orally administered isobutanol was excreted as unchanged isobutanol within 40 hours after administration to rabbits (Saito, 1975).

In lifetime studies, rats given isobutanol by gavage at 0.2 mℓ/kg (160 mg/kg) 2 days/week or subcutaneously at 0.05 mℓ/kg (40 mg/kg) 2 days/week had increased incidences of total tumors, relative to controls; however, no significant increase of any particular tumor type was observed (Gibel et al., 1974, 1975). Therefore the data are inadequate to assess the carcinogenicity of isobutanol. Hilscher et al. (1969) showed that isobutanol could induce reverse mutation in Escherichia coli without metabolic activation. Although no studies regarding the effects of isobutanol on mammalian reproduction were located in the available literature, Clegg (1964) observed embryolethality in chicken eggs treated with the alcohol.

In the carcinogenicity study by Gibel et al. (1974, 1975), rats treated orally with 0.2 mℓ/kg (160 mg/kg) 2 days/week until they died had a markedly lower mean survival time than did controls. Non-neoplastic lesions, including necrosis and fatty degeneration of the liver, cirrhosis and hepatitis, appeared to be treatment-related.

Rats exposed to a 2 M concentration of isobutanol in drinking water for 2 months had gastric and intestinal hemorrhage, decreased liver-to-body weight ratios, decreases in fat, glycogen and RNA content of the liver and smaller hepatocytes (Hillbom et al., 1974a,b). Mallory's alcoholic hyaline bodies also appeared in some livers. Rats treated at 1 M isobutanol for up to 6 months had gastrointestinal bleeding but no liver effects. There were no changes in food consumption or body weight gain with administration of 1 M for up to 6 months or 2 M for 2 months, although isobutanol consumption and caloric intake increased relative to control rates. It was suggested that the isobutanol-induced damage to the gastrointestinal mucosa resulted in decreased food absorption and that the liver pathology may be secondary to the poor nutritional state of the treated rats. In a 13-week oral study (Toxicity Research Laboratory, 1986) rats consuming $\leq$316 mg/kg/day of isobutanol did not have any adverse effects pertinent to body weight changes, or clinical and histopathological parameters, whereas consumption of 1000 mg/kg/day produced hypoactivity and ataxia. Seitz (1972) reported vertigo, headache, and nausea as symptoms of individuals occupationally exposed to isobutanol.

Acute oral LD_{50} values in various species range from 2460-3750 mg/kg (Kushneva et al., 1983; Smyth et al., 1954). Effects after acute intoxication appear primarily related to narcosis (Browning, 1965; Maickel and McFadden, 1979). Blood changes and delayed hepatotoxicity and thyroid

function have also been reported (Kushneva et al., 1983). Isobutanol had a toxic influence on a variety of biological parameters, including destruction of myelin sheath in vitro (Rumsby and Finean, 1966), loss of the righting reflex in mice (McComb and Goldstein, 1975), induction of ataxia in rats (McCreery and Hunt, 1978), inhibition of neurotransmitter uptake in vitro (Roach et al., 1973; Rogawski et al., 1974), inhibition of protein synthesis in vitro (David et al., 1983) and blockade of active transport processes in everted rat intestinal sacs (Chang et al., 1967).

Because the carcinogenicity data of Gibel et al. (1974, 1975) were considered to be inadequate for risk assessment, no q_1^* or F factor could be recommended. Isobutanol is most appropriately placed in IARC Group 3. Based on U.S. EPA (1984) proposed guidelines for carcinogen risk assessment, inadequate animal evidence and no human evidence is available for isobutyl alcohol. Thus, the overall weight of evidence classification of Group D, not classifiable as to human carcinogenicity, is suggested for isobutanol. An ADI of 0.3 mg/kg/day (22 mg/day) was derived based on the NOEL of 316 mg/kg/day in rats treated by gavage in the 90-day study by Toxicity Research Laboratory (1986). An RQ of 1000 was derived based on the increased mortality of the rats treated by gavage with isobutanol for life in the study by Gibel et al. (1974, 1975).

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
1.5.	SUMMARY	3
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	4
2.1.	WATER	4
2.1.1.	Hydrolysis	4
2.1.2.	Oxidation	4
2.1.3.	Photolysis	4
2.1.4.	Microbial Degradation	4
2.1.5.	Volatilization	5
2.1.6.	Adsorption	6
2.1.7.	Bioaccumulation	6
2.2.	AIR	6
2.3.	SOIL	7
2.4.	SUMMARY	7
3.	EXPOSURE	9
3.1.	WATER	9
3.2.	AIR	10
3.3.	FOOD	10
3.4.	DERMAL	11
3.5.	SUMMARY	11
4.	PHARMACOKINETCS	12
4.1.	ABSORPTION	12
4.2.	DISTRIBUTION	12
4.3.	METABOLISM	12
4.4.	EXCRETION	14
4.5.	SUMMARY	14
5.	EFFECTS	15
5.1.	CARCINOGENICITY	15
5.2.	MUTAGENICITY	18
5.3.	TERATOGENICITY	18
5.4.	OTHER REPRODUCTIVE EFFECTS	18
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	18
5.6.	OTHER RELEVANT INFORMATION	21
5.7.	SUMMARY	24

TABLE OF CONTENTS (cont.)

		Page
6.	AQUATIC TOXICITY	27
6.1.	ACUTE	27
6.2.	CHRONIC	27
6.3.	PLANTS	27
6.4.	RESIDUES	27
6.5.	OTHER RELEVANT INFORMATION	27
6.6.	SUMMARY	29
7.	EXISTING GUIDELINES AND STANDARDS	30
7.1.	HUMAN	30
7.2.	AQUATIC	30
8.	RISK ASSESSMENT	31
9.	REPORTABLE QUANTITIES	33
9.1.	REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY	33
9.2.	WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY	33
10.	REFERENCES	38
APPENDIX:	LITERATURE SEARCHED	52

LIST OF TABLES

No.	Title	Page
5-1	Incidence of Tumors in Wistar Rats Treated by Gavage with Isobutanol for an Average of 425 days.	16
5-2	Acute LD_{50} and LC_{50} Values for Isobutanol in Various Species	22
6-1	Acute Toxicity Data for Isobutanol.	28
8-1	Cancer Data Sheet for Derivation of q_1^*	33
9-1	Toxicity Summary for Isobutanol in Wistar Rats.	34
9-2	Oral Composite Scores for Isobutanol in Wistar Rats	35
9-3	Isobutanol: Minimum Effective Dose (MED) And Reportable Quantity (RQ)	36

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BOD	Biological oxygen demand
BODT	Biological oxygen demand, theoretical
bw	Body weight
CAS	Chemical Abstract Service
CHO	Chinese hamster ovary
CS	Composite score
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
ED_3	Effective dose to 3% of recipients
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LC_{LO}	Lowest lethal concentration to recipients
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
ppm	Parts per million
RD_{50}	Concentration necessary to depress the respiratory rate by 50%
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value

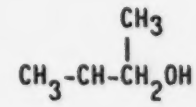
LIST OF ABBREVIATIONS (cont.)

TLV	Threshold limit value
TWA	Time-weighted average
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Isobutanol is known by the synonyms isobutyl alcohol, 2-methyl-1-propanol and isopropyl carbinol (Verschueren, 1983). The structure, molecular weight, chemical formula and CAS number for isobutanol are as follows:



Molecular formula: $C_4H_{10}O$

Molecular weight: 74.12

CAS Registry No.: 78-83-1

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Isobutanol is a colorless liquid with a sweet musty odor that can be perceived as either pleasant or unpleasant (Verschueren, 1983). It is miscible with ethanol and ether (Rowe and McCollister, 1982).

Selected physical and chemical properties are as follows:

Melting point:	-180°C	Verschueren, 1983
Boiling point:	108°C	Verschueren, 1983
Vapor pressure: at 20°C	10.0 mm Hg	Mackay and Yeun, 1983
Water solubility: at 20°C	94,874 mg/ℓ	Rowe and McCollister, 1982
Log K_{ow}:	0.76	Hansch and Leo, 1981
Specific gravity:	0.806	Hawley, 1981
Flashpoint (open cup):	37.7°C	Hawley, 1981
TLV (ACGIH standard):	50 ppm	ACGIH, 1980
(OSHA standard):	100 ppm	

1.3. PRODUCTION DATA

As of January 1985, isobutanol was manufactured commercially by the following U.S. companies (SRI, 1985):

Badische Corp., Freeport, TX
Celenese Corp., Bay City TX and Bishop, TX
Eastman Kodak Co., Longview, TX
Shell Oil Co., Deer Park, TX
Union Carbide Corp., Texas City, TX and Penulas, Puerto Rico

During 1984, 163.15 million pounds of isobutanol were produced in the United States (USITC, 1985). The major U.S. importers of isbutanol in 1977 as listed in the TSCA Inventory were: Nissho-Iwai American Corp., Air Products and Chemicals, Inc. and Steuber Co., Inc., importing between 1-10 million pounds each. Ten other companies also imported small amounts of this chemical in 1977 (U.S. EPA, 1977). In 1981, 14 million pounds of isobutanol were imported into the United States (TSCA-ITC, 1980).

All isobutanol is manufactured as a by-product of the oxo process that involves oxidation of natural gas hydrocarbons (SRI, 1985), although isobutanol can be obtained commercially as a by-product of high-pressure methanol synthesis (Rowe and McCollister, 1982). In the oxo process, propylene is reacted with carbon monoxide to produce n- and iso-butyraldehyde. The aldehydes are then separated and reduced to the corresponding alcohols. Approximately 25% isobutanol and 75% n-butanol are produced by this process (Sherman, 1978).

1.4. USE DATA

Isobutanol is used as an end use solvent (surface coatings, adhesives, cleaning solvents and varnish remover); an intermediate for isobutyl amines (used for herbicides); an intermediate for isobutyl acetate (used as a solvent, flavoring material and in perfume); an intermediate for acrylate

and methacrylate; and an intermediate for amino resins (such as urea-formaldehyde resins) and other esters (TSCA-ITC, 1980; Lawler, 1977; Windholz, 1983). Other end-use solvent applications are as a diluent for brake fluids and extractant in the manufacture of antibiotics, hormones and vitamins (Sherman, 1978). Isobutanol is also a registered ingredient in pesticides (U.S. EPA, 1979).

1.5. SUMMARY

Isobutanol is a colorless liquid with a sweet musty odor. It is miscible with ethanol and ether but is partially soluble in water (Verschueren, 1983; Rowe and McCollister, 1982). SRI (1985) reports that isobutanol was produced in 1984 by five U.S. companies at seven locations. In 1984, 163.15 million pounds of isobutanol were produced in the United States (USITC, 1985) and in 1981, 14 million pounds were imported (TSCA-ITC, 1980). Isobutanol is made commercially as a by-product of the oxo process (SRI, 1985). Primary uses are as a solvent and intermediate (TSCA-ITC, 1980; Lawler, 1977; Windholz, 1983).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. WATER

2.1.1. Hydrolysis. The only pertinent data regarding the hydrolysis of isobutanol located in the available literature was that alcohols are generally resistant to hydrolysis (Lyman et al., 1982).

2.1.2. Oxidation. The rate constants for the reaction between isobutanol and hydroxyl radicals in aqueous solutions (at 15-25°C) have been reported as 2.0×10^9 M^{-1} sec^{-1} (Anbar and Neta, 1967) and 3.3×10^9 M^{-1} sec^{-1} (Dorfman and Adams, 1973). The hydroxyl reaction half-life has been estimated to be 401 and 243 days, respectively, using an approximate OH• radical concentration in water of 10^{-17} M (Mill et al., 1980). Thus, reaction with hydroxyl ions in ambient waters would not be environmentally significant. Data on the reaction of peroxy radicals with aquatic isobutanol could not be located in the available literature.

2.1.3. Photolysis. Pertinent data regarding the photolysis of isobutanol in water could not be located in the available literature as cited in the Appendix.

2.1.4. Microbial Degradation. In a river die-away test on 3 ppm isobutanol at 18-19°C, the degradation of isobutanol in 4 days amounted to 56% of the BOD for the compound (Hammerton, 1955). Price et al. (1974) used a settled wastewater seed to examine biodegradation of isobutanol in freshwater, and measured 5-, 10-, 15- and 20-day BODTs of 46, 71, 75 and 81%, respectively. In a similar study, Heukelekian and Rand (1955) measured a 5-day BODT of 64%.

Yonezsuwa and Urushigawa (1979) determined a biodegradation rate constant of 0.0115 $hour^{-1}$ using activated sludge under aerobic conditions.

Therefore, the biodegradation half-life for isobutanol has been calculated to be 2.5 days. Results of the MITI test categorize isobutanol as a chemical that is "well biodegradable," indicating that the oxygen consumption exceeds 30% after 2 weeks of incubation (Sasaki, 1978). According to two studies, 100 ppm isobutanol incubated with activated sludge was biodegraded 30-100% at the end of 14 days (Kawasaki, 1980; Sasaki, 1978). Dias and Alexander (1971) used domestic sewage as inoculum for testing biodegradability of isobutanol at 25°C. Samples of isobutanol were incubated for 2, 5, 10 and 30 days with resulting BODTs of 42, 61, 71 and 55%, respectively. Gerhold and Malaney (1966) incubated 500 ppm isobutanol with activated sludge for 6, 12 and 24 hours, and observed respective BODTs of 8.3, 18.1 and 32.5%. Other studies using acclimated sludge resulted in 44-100% biodegradation of isobutanol over periods ranging from 4 hours to 5.8 days (Bridie et al., 1979a; McKinney and Jeris, 1955; Hatfield, 1957; Langley, 1970). With nonacclimated sludge, Bridie et al. (1979a) measured a 5-day BODT of 16%. McKinney and Jeris (1955) reported that microbial oxidation of isobutanol results in the formation of isobutyraldehyde, which is further oxidized to isobutyric acid and then possibly to carbon dioxide and water. Little data was found in the existing literature on the biodegradability of isobutanol in natural bodies of water.

2.1.5. Volatilization. Pertinent data regarding the volatilization of isobutanol could not be located in the available literature as cited in the Appendix; however, predictions about its volatilization can be made from the vapor pressure and solubility data for isobutanol. Hine and Mookerjee (1975) provided structure-based bond-contribution and group-contribution methods for estimating Henry's Law constant. The values derived from these methods were 1.1×10^{-5} and 1.15×10^{-5} atm·m³/mol, respectively. Using

vapor pressure and solubility data, Mackay and Yeun (1983) calculated Henry's Law constant to be 1.03×10^{-5} atm·m³/mol. These values for Henry's Law constant suggest that the volatilization of isobutanol may be significant in bodies of water in the absence of other faster degradation processes (Lyman et al., 1982).

2.1.6. **Adsorption.** Pertinent data regarding the adsorption of isobutanol to sediments could not be located in the available literature as cited in the Appendix. The relatively high WS and low K_{ow} of isobutanol suggest that adsorption to suspended organic matter and sediments will not be environmentally significant.

2.1.7. **Bioaccumulation.** Experimental bioaccumulation data could not be located in the available literature. The relatively high WS and low K_{ow} suggest isobutanol is not likely to bioaccumulate. The BCF may be estimated from log K_{ow} using the following equation of Veith (1980): log BCF = 0.76 log K_{ow} - 0.23. The calculated BCF of 2.2 suggests that bioaccumulation is not important.

2.2. AIR

Dilling et al. (1976) studied the photodecomposition rate of isobutanol under simulated atmospheric conditions. In the presence of 5 ppm nitrous oxide, 10 ppm isobutanol had a half-life of 3.5 hours. Farley (1977) classified isobutanol as a moderately reactive compound in the atmosphere, based on information collected from smog chamber studies. An experimentally determined rate constant for the reaction of isobutanol with hydroxyl radicals in air was not located; however, Guesten et al. (1981) derived a method of estimating vapor phase rate constants from values derived in aquatic media. Thus, the vapor phase half-life for the OH· radical reaction was determined to be 21.4 and 38.5 hours from rate constants of

3.3×10^9 M^{-1} sec^{-1} (Dorfman and Adams, 1973) and 2.0×10^9 M^{-1} sec^{-1} (Anbar and Neta, 1967), respectively. The rate constant for OH• reaction with 1-butanol in the gas phase is 7.32×10^{-12} cm^3 $molecule^{-1}$ sec^{-1} (Atkinson, 1985). Assuming the OH• radical concentration of 10^6 molecule cm^{-3} in the troposphere, the half-life is estimated as 26 hours. Since isobutanol is structurally similar to 1-butanol, the atmospheric OH• reaction is expected to produce a similar half-life.

2.3. SOIL

Pertinent data regarding the environmental fate and transport of isobutanol could not be located in the available literature as cited in the Appendix. The relatively low K_{ow} and high WS of isobutanol suggest leaching as a possible transport mechanism. Following the molecular topology and quantitative-structure analysis method of Sabljic (1984), the K_{oc} was estimated to be 50. Using the following equation from Lyman et al. (1982): Log K_{oc} = -0.55 log S + 3.64, the K_{oc} was calculated to be 8.5. Based on these approximations, isobutanol should be highly mobile in soil (Swann et al., 1983). Drawing an analogy from its behavior in aquatic media, the author predicted that hydrolysis in soil will be an insignificant process; however, volatilization from soil surfaces and biodegradation may play a significant role in determining the fate of this compound in soil.

2.4. SUMMARY

In ambient water, hydrolysis and oxidation of isobutanol by hydroxyl radicals are not expected to be important reaction processes. In activated sludge systems, isobutanol has been significantly biodegraded. Although no data on the biodegradability of isobutanol in natural aquatic media are available, the results of biodegradation in activated sludge can be used to predict that significant biodegradation will occur in natural waters.

Volatilization of isobu anol may be significant in aquatic media (Lyman et al., 1982). The relativ ly low K_{ow} and high WS suggest that adsorption to sediments and bioconcentr tion in aquatic organisms are unlikely.

In the atmosphere, rea tions with OH• and NO_x are likely to be the significant fate processes for isobutanol. Its half-life (because of OH• reaction) is expected to e >1 day. Removal of atmospheric isobutanol through dry deposition and adsorption onto particulate matters and subsequent deposition are likely to be insignificant. Because of its reasonably high WS, wet deposition may be somewhat significant in removing atmospheric isobutanol.

Based on its behavior in aquatic media, it is predicted that both volatilization and biodegrad tion processes will play important roles in the loss of isobutanol from so l. The estimated K_{oc} data also indicate that isobutanol should be highly obile in soil.

3. EXPOSURE

The general population is exposed almost continuously to low levels of "natural" isobutanol (U.S. EPA, 1983). Natural isobutanol is produced by the fermentation of carbohydrates (Windholz, 1983). The fermentation may be a controlled process, as in the production of alcoholic beverages and foods such as cheeses, or uncontrolled, as in the decay of materials in a municipal waste plant or dump (U.S. EPA, 1983). Because of the ubiquitous nature of the fermentation of carbohydrates, the presence of naturally occurring isobutanol is likely to be more widespread in the environment than industrially generated isobutanol, although much higher concentrations evolve at sites where isobutanol is produced, processed or used than in nature (U.S. EPA, 1983).

3.1. WATER

The U.S. EPA STORET Data Base has no recorded monitoring data for isobutanol. Isobutanol has been identified at levels ranging between 142 and 652 ppm in Hayashida River water, which contained effluents from the leather industry (Yasuhara et al., 1981). Isobutanol has also been identified as a constituent of petrochemical wastewater (SRC, 1980) and palm mill effluents (Hwang et al., 1978). Serious contamination of the groundwater ~30 M below a paint factory was found to have resulted from leakage of solvent from underground storage tanks (Botta et al., 1984). Identification of isobutanol in the leachate from a model landfill (Burrows and Rowe, 1975) suggests isobutanol may enter groundwater from landfill leachates (U.S. EPA, 1983).

3.2. AIR

Atmospheric emmissions of isobutanol result from volatilization from a variety of sources, including whiskey fermentation units (Carter and Linsky, 1974), waste treatment units (Hangartner, 1979), palm mill effluent (Hwang et al., 1978), animal wastes (Yasuhara et al., 1984; Graedel, 1978), plants, microbes, solvent use, and petroleum manufacturing and storage (Graedel, 1978). Uncontrolled emissions from vacuum systems used during the concentration, separation and rectification in the manufacturing of synthetic aromatics contained 580 mg/m^3 isobutanol (Kondakova et al., 1982). Carter and Linsky (1974) detected $\leq$2.5 mg/m^3 isobutanol in emissions from whiskey fermentation vats. Yasuhara et al. (1984) detected 0.13 µg/g isobutanol in fresh swine manure. As a result of evaporation of solvent, industrial isobutanol is more likely to be released to the atmosphere and at higher concentrations than naturally produced isobutanol (U.S. EPA, 1983). It has been estimated that ~375,000 people are occupationally exposed to isobutanol annually (U.S. EPA, 1983).

3.3. FOOD

Isobutanol has been identified as a volatile compound in the flavor component of fried chicken coated with 2% flour and fried in shortening consisting of 90% beef fat and 10% cotton seed oil (Tang et al., 1983). Isobutanol has been identified in apples, prickly pear pads, dried bonito, dried foliage of cryptotaenia japonica and in gases volatilizing from potatoes in storage (SRC, 1980; U.S. EPA, 1983). Isobutanol is also found in most alcoholic beverages such as wine, distilled alcoholic beverages and various whiskeys at levels up to 1 g/ℓ (U.S. EPA, 1983).

3.4. DERMAL

Dermal exposure may result from the use of products containing isobutanol such as surface coatings (paint) and brake fluids (Luedersdorf et al., 1985; TSCA-ITC, 1980).

3.5. SUMMARY

The general population is almost continuously exposed to low levels of "natural" isobutanol (U.S. EPA, 1983), which is produced by the fermentation of carbohydrates (Windholz, 1983); thus, isobutanol can enter air, water and food from a variety of sources. Higher concentrations of isobutanol, however, are expected to evolve from sites where isobutanol is produced, processed or used rather than from nature (U.S. EPA, 1983). Isobutanol has been monitored in river water and in one groundwater sampling area (Yasuhara et al., 1981; Botta et al., 1984). Several sources of emissions into air have been reported, including volatilization from palm mill effluent (Hwang et al., 1978), petrochemical processes and storage, solvent use and animal wastes (Graedel, 1978; Yasuhara et al., 1984).

Isobutanol has been found in various edible items, including some fruit (SRC, 1980), fried chicken (Tang et al., 1983) and most alcoholic beverages (TSCA-ITC, 1980).

Dermal exposure may result primarily from the use of products containing isobutanol as a solvent or during its direct use as a solvent (Leudersdorf et al., 1985; U.S. EPA, 1983).

4. PHARMACOKINETICS

4.1. ABSORPTION

Browning (1965) reported that isobutanol can be readily absorbed through the lungs and gastrointestinal tract. Peak blood levels of 0.5 mg/mℓ isobutanol were observed 1 hour after administration of an oral dose of 2 mℓ/kg (~1600 mg/kg) to rabbits (Saito, 1975). Bonte et al. (1981) reported a maximum blood level of isobutanol of 0.28 mg/ℓ in humans immediately after drinking a mixture of orange juice, 5-40% ethanol and 1 g/ℓ of isobutanol.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of isobutanol could not be located in the available literature as cited in the Appendix.

4.3. METABOLISM

Saito (1975) gave 2 mℓ/kg isobutanol to male rabbits by gavage followed by drinking water saturated with isobutanol (concentration and duration not specified). The urine was collected for an unspecified period and analyzed for metabolites. The metabolites were identified as acetaldehyde, acetic acid, isobutyraldehyde and isovaleric acid. A small amount of unchanged isobutanol was also found in the urine. The rate of isobutanol oxidation was reported to be intermediate between propanol and ethanol. Saito (1975) proposed a pathway in which isobutanol is oxidized by alcohol dehydrogenase to isobutyraldehyde, which in turn is oxidized to isobutyric acid, which reacts with Coenzyme A, thereby entering the tricarboxylic acid cycle with the subsequent liberation of CO_2.

Involvement of the tricarboxylic acid cycle in the metabolism of isobutanol is supported by the work of Hedlund and Kiessling (1969), who

demonstrated that the activity of isobutyraldehyde dehydrogenase, the enzyme that catalyzes the oxidation of isobutyraldehyde to isobutyric acid, is located in the fraction of rat liver homogenate.

Kamil et al. (1953) administered isobutanol by gavage to chinchilla rabbits weighing 3 kg at a dose of 25 mmol/rabbit (~618 mg/kg) and found 4.4% of the dose as a glucuronide acid conjugate in the urine collected for 24 hours after dosing. Excretion of glucuronic acid conjugate was essentially complete at this time. No aldehydes or ketones were detected in urine. Furthermore, no aldehydes or ketones were detected in the expired air of a rabbit that was dosed orally with 6 mℓ isobutanol (~1600 mg/kg). The failure of Kamil et al. (1953) to find aldehydes in the urine is in contrast with the findings of Saito (1975). Although it is not clear from the report by Kamil et al. (1953) whether the urine analyzed for aldehydes was collected from the rabbits dosed with ~618 mg/kg or from the rabbit dosed with ~1600 mg/kg, the difference in the findings of the investigators may be due to differences in the amounts administered. Following the single gavage dose of ~1600 mg/kg, the rabbits in the Saito (1975) study were given drinking water saturated with isobutanol, whereas the rabbit in the Kamil et al. (1953) study received only a single dose of ~1600 mg/kg.

The rate of isobutanol oxidation was also studied by Hedlund and Kiessling (1969), using both a rat liver homogenate and a liver perfusion system (Wistar rats were used). The homogenate (5 mℓ of 0.25 g liver/mℓ) oxidized 80 µmols of isobutanol at a rate ~7 µmol/g liver/min, while the perfused liver oxidized 5.3 µmols of isobutanol at a rate ~2 µmol/g liver/min. Addition of the alcohol dehydrogenase inhibitor, pyrazole, inhibited the <u>in vitro</u> oxidation by 65%. Lester and Benson (1970) observed that pyrazole inhibited isobutanol oxidation by ~50% in Sprague-Dawley rats.

4.4. EXCRETION

After a single oral administration in rabbits (see Sections 4.1. and 4.3.), Saito (1975) noted a slow rate of urinary excretion of isobutanol and its metabolites. The blood level of isobutanol reached a maximum 1 hour after dosing and declined to undetected at 6 hours. Of the administered dose, <0.5% was excreted in the urine or breath as unchanged isobutanol 40 hours after administration.

In another study involving oral dosing, Kamil et al. (1953) administered 25 mmol (~618 mg/kg) isobutanol by gavage to rabbits. The excretion of the glucuronide conjugate (4.4% of the total dose) was complete within 24 hours.

Bonte et al. (1981) noted that a blood level of isobutanol of 0.28 mg/ℓ in humans immediately after drinking a mixture of orange juice, ethanol and isobutanol (see Section 4.1.) had dissipated 12 hours later.

4.5. SUMMARY

Isobutanol is readily absorbed through gastrointestinal and pulmonary mucosa (Browning, 1965; Saito, 1975; Bonte et al., 1981). It is metabolized to isobutyraldehyde and then to isobutyric acid, which may enter the tricarboxylic acid cycle by a Coenzyme A-mediated pathway (Saito, 1975). While Saito (1975) detected unchanged isobutanol, acetaldehyde, acetic acid, isobutyraldehyde and isovaleric acid in the urine of rabbits dosed orally with isobutanol, Kamil et al. (1953) failed to detect aldehydes in the urine or breath of orally dosed rabbits. Excretion of a glucuronide conjugate in the urine, however, accounted for 4.4% of the dose (Kamil et al., 1953) and was complete within 24 hours. Analysis of urinary or breath data suggested that a negligible fraction of orally administered isobutanol was excreted as unchanged isobutanol 40 hours after administration to rabbits (Saito, 1975).

5. EFFECTS

5.1. CARCINOGENICITY

Two reports of the same study were located in the available literature regarding the carcinogenicity of isobutanol (Gibel et al., 1974, 1975). Nineteen Wistar rats of unspecified sex were administered an oral dose of 0.2 mℓ/kg (160 mg/kg) isobutanol twice weekly from 70 days of age until death. An additional group of 24 rats was given 0.05 mℓ/kg (40 mg/kg) isobutanol subcutaneously twice weekly. The isobutanol was double distilled. Groups of 25 rats each were maintained on the same oral or subcutaneous schedule, but were given normal saline rather than isobutanol. At necropsy, all animals were examined histologically for "benign" and "malignant" tumors and non-neoplastic insult. In addition to histological examination of "all organs," the vertebrae and femur, differential blood counts, blood smears and leukocyte counts were performed.

The mean survival time for both groups of controls was >643 days, at which time all remaining controls were sacrificed. For those rats dosed orally or subcutaneously with isobutanol, mean survival times were 495 and 544 days, respectively. In the oral controls, 3/25 rats had benign tumors and, of those injected subcutaneously, 2/25 had benign tumors. The benign tumors in controls were small papillomas and mammary fibroadenomas. No malignant tumors were observed in either control group. In the group treated orally with isobutanol, 9/19 had benign tumors and 3/19 had malignancies; the three malignancies were a forestomach carcinoma, a liver cell carcinoma, and a forestomach carcinoma and myeloid leukemia. The results of the oral dosing experiment are summarized in Table 5-1. In the group treated subcutaneously with isobutanol, 3/24 rats had benign tumors and 8/24

TABLE 5-1

Incidence of Tumors in Wistar Rats Treated by Gavage with Isobutanol for an Average of 425 days[a,b]

Dose	Target Organ	Tumor Type	Tumor Incidence (p value)[c]
0.0 mℓ/kg, 2 times/week	various	benign[d]	3/25
0.2 mℓ/kg, 2 times/week	various	benign[e]	9/19 (p=0.011)
0.0 mℓ/kg, 2 times/week	various	malignant	0/25
0.2 mℓ/kg, 2 times/week	various	malignant[f]	3/19 (p=0.073)
0.0 mℓ/kg, 2 times/week	various	benign or malignant[g]	3/25
0.2 mℓ/kg, 2 times/week	various	benign or malignant[g]	12/19 ($p=5.4\times10^{-4}$)

TABLE 5-1 (cont.)

QUALITY OF EVIDENCE	
Strengths of Study:	The chemical was given by a relevant route for the lifespan and histopathological examinations were performed on major organs.
Weakness of Study:	Few rats in each group; only one dose level used; dosing was only twice weekly; sex not specified; only one species studied.
Overall Adequacy:	Inadequate
Comments:	A separate subcutaneous study supported the results of oral dosing regarding the increased carcinogenic risk.

[a]Source: Gibel et al., 1974, 1975

[b]The mean duration of the study was equivalent to the average survival time of the isobutanol-treated animals, minus the first 70 days of life (see Text). Controls were treated with physiological saline on an average of 573 days.

[c]Fischers Exact Test performed at SRC.

[d]Control rats exhibited only mammary fibroadenomas and papillomas of the forestomach.

[e]The following tumors were typically found in treated rats, although it was unclear which experimental alcohol induced which growths: stomach and kidney adenomas, splenic fibromas, pancreatic adenomas, papillomas of the forestomach, etc.

[f]Forestomach carcinoma and hepatocyte carcinoma; forestomach carcinoma and myeloid leukemia; myeloid leukemia

[g]Assuming that the rats with benign tumors did not also have malignant tumors.

had malignant tumors. These eight malignancies included two forestomach carcinomas, two hepatic sarcomas, two retroperitoneal sarcomas, a splenic sarcoma and a mesothelioma.

5.2. MUTAGENICITY

The only study located in the available literature regarding the mutagenicity of isobutanol was by Hilscher et al. (1969). Escherichia coli CA274 cells were suspended in a salt solution at a concentration of 10^{10} cells per mℓ. A 72-hour incubation with 2.5% isobutanol was followed by plating on a tryptophan-containing minimal medium. Isobutanol caused a 7-fold increase in tryptophan$^-$ to tryptophan$^+$ reversions. No metabolic activating system was used.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of isobutanol in mammalian species could not be located in the available literature as cited in the Appendix. As cited in U.S. EPA (1983) and TSCA-ITC (1980), however, an injection of 0.05 mℓ isobutanol into the yolk sacs of 5-day incubated chicken eggs was lethal to 6/6 eggs (Clegg, 1964). Developing embryos also died when the eggs were immersed in isobutanol; however, because the doses were lethal, teratogenic effects could not be assessed.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of isobutanol could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In the carcinogenicity bioassays discussed in Section 5.1., Gibel et al. (1974, 1975) described a number of non-neoplastic effects that apparently occurred in rats treated with isobutanol, as well as in rats treated with other alcohols. These lesions included hyperplasia of the bone marrow

parenchyma, metaplasia in the liver and spleen, heart muscle necrosis, interstitial pancreatitis and fibrosis, and hepatic necrosis and fatty degeneration, cirrhosis and hepatitis. Although it was not clear if these lesions also occurred in controls, it was implied that the lesions were alcohol-induced. The mean survival time of the rats treated orally with isobutanol was 495 days, compared with >643 days for the controls.

Hillbom et al. (1974a,b) conducted a series of subchronic experiments using rats. In the first experiment, a group of five male Wistar rats, 4 months old at initiation, were given a 2 M (148 g/ℓ) solution of isobutanol as the sole drinking source for 2 months. In the second study, a group of six male rats was given a 1 M (74 g/ℓ) solution of isobutanol as the only drinking source for 4 months. In each of the two experiments, all rats were sacrificed after the treatment period for histological examination. A third experiment involved administration to 11 male rats of 1 M isobutanol as the only drinking source for 6 months. At the end of this time, five rats were sacrificed for liver pathology and the remainder were kept on tap water for 1 month more before sacrifice. Rats given only tap water served as controls. Fluid and caloric intake, food consumption, body weights and liver weights were measured, and histological examinations of livers were performed. No other organs were microscopically examined.

In these experiments, neither the 1 M nor the 2 M solutions had any effect on food consumption or body weight gain. These dose regimens, however, markedly increased isobutanol consumption and, therefore, total caloric intake. For the group receiving 1 M isobutanol, fluid intake increased from 6.5 to 12.6 mmol/100 kg/day from the start to the end of the 4-month period. To determine the nature of the increased isobutanol consumption, Hillbom et al. (1974a) conducted an experiment in which rats were given isobutanol as a sole drinking fluid (forced-choice) followed by a

choice of isobutanol or tap water (free-choice). For the free-choice period, isobutanol consumption decreased significantly ($p>0.001$), while food consumption increased significantly ($p<0.001$) compared with the forced-choice period. Thus, no dependence on isobutanol developed and caloric intake remained high or increased. Effects on the liver were observed only in the rats given 2 M isobutanol for 2 months. These effects included decreased liver-to-body weight ratios ($p<0.005$) and decreases in fat, glycogen, RNA content and overall hepatocyte size. Mallory's alcoholic hyaline bodies were observed in the livers of some rats given 2 M isobutanol. At both the 1 M and 2 M levels, rats had increased incidences of small intestinal and gastric mucosal bleeding and enlarged gas- or food-filled stomachs or both.

As food consumption and body weight gain were not affected but isobutanol and caloric intake were increased, Hillbom et al. (1974a,b) suggested that isobutanol had an effect on food absorption, perhaps secondary to the gastrointestinal damage. Because the liver pathology in the rats given 2 M isobutanol for 2 months was not observed in the rats given 1 M isobutanol for up to 6 months, it is possible that the liver lesions were secondary to the more impaired nutritional state of the rats drinking 2 M isobutanol.

Only one study of repeated inhalation exposure to isobutanol was observed. Inhalation exposure of mice to 2125 ppm (6442 mg/m^3) for 9.25 hours/exposure for a total of 223 hours did not result in any deaths (Weese, 1928). Repeated exposure to 6400 ppm (19,400 mg/m^3) for an unspecified duration resulted in repeated transient narcosis.

Because of the lack of adequate oral toxicity data for isobutanol, the U.S. EPA's Office of Solid Waste, under the RCRA land disposal ban, contracted to the Toxicity Research Laboratory (1986) to conduct 90-day subchronic studies in rats to generate toxicity data for risk assessment.

Four groups of male and female rats (30/sex/group) were dosed daily by gavage with 0, 100, 316 and 1000 mg/kg/day of isobutyl alcohol for 13 weeks. Six weeks after the initiation of dosing, an interim sacrifice of 10 rats/sex was performed to evaluate clinical, biochemical, gross and morphological changes in target organs. Remaining animals continued in the experiment until the day of final sacrifice (day 92 or 93). Additional data from this included body and organ weight changes, food consumption, morbundity, mortality, ophthalmological and gross and histopathological examinations. An evaluation of the data revealed no effect on body weight, or clinical and histopathological parameters at doses of $\leq$316 mg/kg/day. Treatment at the high-dose (1000 mg/kg/day) resulted in a minor decrease in body weight gain during week 2 and decreased serum potassium levels and hypoactivity, which was the most frequently observed clinical sign. Hypoactivity occurred in every rat in the high-dose group during week 1, was markedly decreased by week 4 and occurred only sporadically thereafter. Ataxia occurred at a low incidence in the high-dose group throughout the study.

Seitz (1972) described four cases of laboratory workers occupationally exposed to isobutanol. The duration of exposures ranged from very short term to 18 months. The workers generally complained of vertigo, nausea, and headache; one case was diagnosed as vestibular irritation and another as Meniere's disease. No other details were provided.

5.6. OTHER RELEVANT INFORMATION

Values for the acute LD_{50} and LC_{50} of isobutanol are presented in Table 5-2. Kushneva et al. (1983) observed reduced numbers of granulocytes and lymphocytes, alterations in the number of splenocytes, increased thyroid activity, and hepatic functional changes in animals variously exposed to isobutanol. Maickel and McFadden (1979) suggested that immediate narcosis

TABLE 5-2

Acute LD_{50} and LC_{50} Values for Isobutanol in Various Species

Species	Route	LD_{50} or LC_{50}	Reference
Mouse	oral	3,500 mg/kg	Kushneva et al., 1983
Mouse	inhalation	15,500 mg/m³	Kushneva et al., 1983
Mouse	intraperitoneal	544 mg/kg (7 days)	Malckel and McFadden, 1979
Mouse	intraperitoneal	21,000 mg/kg (30 mm)	Malckel and McFadden, 1979
Rat	oral	3,100 mg/kg	Kushneva et al., 1983
Rat	oral	2,460 mg/kg	Smyth et al., 1954
Rat	inhalation	19,200 mg/m³	Kushneva et al., 1983
Rabbit	oral	3,750 mg/kg	Smyth et al., 1954
Rabbit	inhalation	26,250 mg/m³	Kushneva et al., 1983
Rabbit	skin	3,392 mg/kg	Smyth et al., 1954
Guinea pig	inhalation	19,900 mg/m³	Kushneva et al., 1983

and delayed hepatotoxicity occurs in Swiss-Webster mice parenterally dosed with isobutanol. A single oral dose as high as 4 g/kg isobutanol had no effect on hepatic weights, nor on triglyceride, cholesterol, or phospholipid content in female Wistar rats sacrificed 17 hours after dosing (Gaillard and Derache, 1966). DeCeaurriz et al. (1981) determined the RD_{50} (concentration that produced a reflex decrease of 50% in the respiratory rate) in six male Swiss OF_1 mice exposed by inhalation to isobutanol vapors to be 1818 ppm (~5510 mg/m³).

Isobutanol has been found to exert varied effects on the nervous system. In vitro, the alcohol was found to completely disorganize the myelin sheath of rat sciatic nerve preparations, and to often lead to a severe axonal degeneration (Rumsby and Finean, 1966). When injected intraperitoneally in mice, isobutanol was about 5 times as potent as ethanol in effecting loss of the righting reflex (McComb and Goldstein, 1975). Similarly, McCreery and Hunt (1978) found isobutanol 5-6 times more potent than ethanol in inducing ataxia in male Sprague-Dawley rats. These authors injected groups of rats with one of several doses of an alcohol, then scored the subsequent motor response between 0 (normal) and 7 (dead). A score of 3 (described as the presence of pronounced impairment of gait and motor incoordination, but with elevated abdomen and pelvis), or ED_3, was compared across a series of alcohols. The ED_3 for ethanol was 32.6 mmol/kg and for isobutanol was 5.4 mmol/kg. McCreery and Hunt (1978) noted that the ED_3 decreased (and potency increased) up to an alcoholic chain length of 6-8 carbon atoms.

The effects of various alcohols in inhibiting neurotransmitter uptake in rat brain synaptosomal preparations have been explored in two studies. A concentration of 1.5% v/v isobutanol was found to inhibit [^{3}H]-norepinephrine uptake by about 75% (Roach et al., 1973). Similarly, tryptophan

hydroxylase activity was found to be inhibited about 50% after treatment with 0.5% w/v isobutanol (Rogawski et al., 1974). It was found that the degree of inhibition of either transmitter uptake or enzyme activity was correlated with the lipophilicity of a particular alcohol. Shoemaker (1981) concluded that alcohols appear to decrease the viscosity of biological membranes, thereby slightly altering transmitter activity.

Chang et al. (1967) also found chain length-dependent effects on amino acid transport characteristics in everted rat intestinal sacs. Test solutions, containing [^{14}C]-labeled amino acids, were placed on either side of the everted sacs. A 1% solution of isobutanol effectively reduced the normal serosal/mucosal concentration balance of [^{14}C]-phenylanine; ethanol was effective only at a 3% concentration. The authors therefore concluded that the longer chain alcohols more effectively inhibited transport mechanisms.

David et al. (1983) prepared postmitochondrial extracts from CHO cells for measurements of protein synthesis after incubation with one of four alcohols. Isobutanol strongly suppressed both mRNA translation and LeutRNA synthetase. The extent of the suppression of protein synthesis was positively associated with chain length in the series methanol → isobutanol.

5.7. SUMMARY

In a lifetime study, rats given isobutanol by gavage at 0.2 mℓ/kg (160 mg/kg) 2 days/week or subcutaneously at 0.05 mℓ/kg (40 mg/kg) 2 days/week had increased incidences of total tumors, relative to controls; however, no significant increase of any particular tumor type was observed (Gibel et al., 1974, 1975). Therefore, the data are inadequate to assess the carcinogenicity of isobutanol. Hilscher et al. (1969) showed that isobutanol could induce reverse mutation in Escherichia coli without metabolic activation.

Although studies regarding the mammalian reproductive effects of isobutanol could not be located in the available literature, Clegg (1964) observed embryolethality in chicken eggs treated with the alcohol.

In the carcinogenicity study by Gibel et al. (1974, 1975), rats treated orally with 0.2 mℓ/kg (160 mg/kg) 2 days/week until they died had a markedly lower mean survival time than did controls. Non-neoplastic lesions, including necrosis and fatty degeneration of the liver, cirrhosis and hepatitis, appeared to be treatment-related.

At a 2 M isobutanol drinking water concentration for 2 months, rats showed gastric and intestinal hemorrhage, decreased liver-to-body weight ratios, decreases in fat, glycogen and RNA content of the liver and smaller hepatocytes (Hillbom et al., 1974a,b); Mallory's alcoholic hyaline bodies also appeared in some livers. Rats given 1 M isobutanol for up to 6 months had gastrointestinal bleeding, but no liver lesions. There were no changes in either food consumption or body weight gain with administration of 1 M for up to 6 months or 2 M for 2 months, although isobutanol consumption and caloric intake increased, relative to control rates. It was suggested that isobutanol-induced damage to the gastrointestinal mucosa resulted in decreased food absorption and that the liver pathology may be secondary to the poor nutritional state of the treated rats. A subchronic oral toxicity study (Toxicity Research Laboratory, 1986) showed that rats given 1000 mg/kg/day isobutyl alcohol by gavage consistently showed hypoactivity and ataxia during the 13-week period. Evaluation of data from this study further revealed no effect on body weight or clinical and histopathological parameters at doses $\leq$316 mg/kg/day. Seitz (1972) reported vertigo, headache and nausea as symptoms of workers occupationally exposed to isobutanol.

Acute oral LD_{50} values in various species have ranged from 2460-3750 mg/kg (Kushneva et al., 1983; Smyth et al., 1954). Effects after acute intoxication appear primarily related to narcosis (Browning, 1965; Maickel and McFadden, 1979), although blood changes and delayed hepatotoxicity and thyroid function have also been reported (Kushneva et al., 1983). Isobutanol had a toxic influence on a variety of biological parameters including the following: destruction of myelin sheath in vitro (Rumsby and Finean, 1966); loss of the righting reflex in mice (McComb and Goldstein, 1975); induction of ataxia in rats (McCreery and Hunt, 1978); inhibition of neurotransmitter uptake in vitro (Roach et al., 1973; Rogawski et al., 1974); inhibition of protein synthesis in vitro (David et al., 1983); and blockade of active transport processes in everted rat intestinal sacs (Chang et al., 1967).

6. AQUATIC TOXICITY

6.1. ACUTE

The available information concerning toxicity of isobutanol to aquatic biota is presented in Table 6-1. Isobutanol is relatively nontoxic to cyprinid fishes and crustaceans in acute exposures, with LC_{50} values >1000 mg/ℓ for all species tested. Pertinent data concerning acute toxicity to other fishes or invertebrates could not be located in the available literature as cited in the Appendix. Bringmann (1978) reported that 296 mg/ℓ was the toxicity threshold for inhibition of cell multiplication in the protozoan Entosiphon subcatum.

6.2. CHRONIC

Only one study concerning chronic sublethal toxicity of isobutanol to aquatic species was found; Hermens et al. (1985) reported that 436 mg/ℓ was a NOEL for growth of Daphnia magna in a 16-day exposure.

6.3. PLANTS

Bringmann and Kuehn (1978) and Bringmann (1978) reported toxicity thresholds of 290-350 mg/ℓ for inhibition of cell multiplication in algae and bacteria (see Table 6-1).

6.4. RESIDUES

Pertinent data regarding isobutanol residues in aquatic biota could not be located in the available literature as cited in the Appendix. Because of its low K_{ow} and rapid biodegradation, isobutanol would not be expected to bioconcentrate in aquatic organisms (TSCA-ITC, 1980).

6.5. OTHER RELEVANT INFORMATION

Gilgan and Burns (1976) reported an LD_{50} of 2-3 mℓ/kg for isobutanol injected into lobsters, Homarus americanus.

TABLE 6-1

Aquatic Toxicity Data for Isobutanol

Species	Concentration (mg/l)	Response	Reference
FISH			
Goldfish (*Carassius auratus*)	2600	24-hour LC_{50}	Bridie et al., 1979b
Fathead minnow (*Pimephales promelas*)	1430	96-hour LC_{50}	Veith et al., 1983
Golden orfe (*Leuciscus idus*)	800, 970	48-hour LC_{50}	Juhnke and Luedemann, 1978
Golden orfe (*Leuciscus idus*)	1520, 1750	48-hour LC_{50}	Juhnke and Luedemann, 1978
Golden orfe (*Leuciscus idus*)	2170, 2240	48-hour LC_{50}	Juhnke and Luedemann, 1978
Bleak (*Alburnus alburnus*)	1000-3000	96-hour LC_{50}	Linden et al., 1979
AMPHIBIANS			
Tadpoles - unspecified	3335-4002	narcotic threshold	Munch, 1972
CRUSTACEANS			
Brine shrimp (*Artemia salina*)	1400	24-hour LC_{50}	Price et al., 1974
Water flea (*Daphnia magna*)	670	24-hour LC_{50}	Bringmann and Kuehn, 1977a
Water flea (*Daphnia magna*)	1220	24-hour LC_{50}	Bringmann and Kuehn, 1977a
PROTOZOA			
Flagellate (*Entasiphon sulcatum*)	296	toxicity threshold, inhibition of cell multiplication	Bringmann, 1978
PLANTS			
Green alga (*Scendescmus quadricauda*)	350	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1978
Blue-green alga (*Microcystis aeruginosa*)	290	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1978
BACTERIA			
Pseudomonas putida	280	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1977b
Photobacterium phosphoreum	1670	5-minute EC_{50} for reduced bioluminescence	Curtis et al., 1982

6.6. SUMMARY

Concentrations of isobutanol acutely toxic to the aquatic species studied are on the order of grams/liter, indicating that isobutanol is relatively nontoxic and unlikely to cause ecological effects in the environment (TSCA-ITC, 1980). Sublethal effects have been reported at lower concentrations, the most sensitive of which was the threshold for cell multiplication inhibition of the bacterium, Pseudomonas putida, at 280 mg/ℓ. The limited information available indicates that isobutanol is not highly toxic to aquatic organisms.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The OSHA permissible exposure limit is 100 ppm, or ~300 mg/m^3, for isobutanol vapor (CFR, 1985). According to the ACGIH (1985), the TLV for isobutanol is 50 ppm (~150 mg/m^3) and the STEL is 75 ppm (~225 mg/m^3). These values were recommended by ACGIH (1980) based on analogy to the slightly less acutely toxic n-butanol, "whose former TLV of 100 ppm was based on its acute toxic response." However, the present value adapted for n-butanol is 50 ppm (150 mg/m^3), which is the ceiling limit rather than the TLV (ACGIH, 1985). Furthermore, ACGIH (1985) intends to delete the STEL for isobutanol and recommends that the STEL of 75 ppm (225 mg/m^3) be used during 1985-1986 proposed change period.

7.2. AQUATIC

Pertinent data regarding aquatic guidelines and standards for isobutanol could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

In a lifetime study, rats given isobutanol by gavage at 0.2 mℓ/kg (160 mg/kg), 2 days/week or subcutaneously at 0.05 mℓ/kg (40 mg/kg) 2 days/week had significantly increased incidences of total tumors, compared with controls (see Table 5-1); however, no significant increase of any particular tumor type was observed (Gibel et al., 1974, 1975). According to the proposed U.S. EPA (1984) Guidelines for Cancer Risk Assessment, these data represent inadequate evidence and, therefore, "cannot be interpreted as showing either the presence or absence of a carcinogenic effect."

Hilscher et al. (1969) showed that isobutanol could induce reverse mutation in Escherichia coli without metabolic activation. Although studies regarding the mammalian reproductive or teratogenic effects of isobutanol could not be located in the available literature, Clegg (1964) observed embryolethality in chicken eggs treated with isobutanol.

In the only chronic study available, rats treated orally with 0.2 mℓ/kg (160 mg/kg) 2 days/week until they died had a markedly lower mean survival time than did the saline-treated controls (Gibel et al., 1974, 1975). Non-neoplastic lesions, including necrosis and fatty degeneration of the liver, cirrhosis and hepatitis, appeared to be treatment-related. Since the statistical significance of these effects was not reported and because of the dosing schedule (2 days/week), these data are inadequate for quantitative risk assessment.

At a 2 M isobutanol drinking water concentration for 2 months, rats had gastrointestinal hemorrhage, decreased relative liver weight, decreased content of fat, glycogen and RNA in the liver and small hepatocytes (Hillbom et al., 1974a,b). Rats given 1 M isobutanol for up to 6 months had gastrointestinal bleeding, but no liver effects. There were no changes in food

consumption or body weight gain with administration of 1 M or 2 M isobutanol, although isobutanol consumption and caloric intake increased. Rats drinking 1 or 2 M isobutanol solutions had enlarged gas- or food-filled stomachs. It was suggested that the isobutanol-induced damage to the gastrointestinal mucosa resulted in decreased food absorption and that the liver pathology may be secondary to the poor nutritional state of the treated rats. Based on data provided by Hillbom et al. (1974a), the rats had consumed ~10 mmol/100 g/day or 7412 mg/kg/day. This dose is 2-3 times higher than the oral LD_{50} values of 2460 mg/kg (Smyth et al., 1954) and 3100 mg/kg (Kushneva et al., 1983) reported for isobutanol in rats. In a 13-week oral study (Toxicity Research Laboratory, 1986) rats consuming 1000 mg/kg/day isobutanol experienced a slight reduction in body weight gain, decreased serum potassium levels, hypoactivity and ataxia. No adverse effects were seen in rats receiving doses $\leq$316 mg/kg/day isobutanol. The level of 316 mg/kg/day is considered a NOEL and 1000 mg/kg/day a LOAEL in rats. The NOEL of 316 mg/kg/day is the most appropriate NOEL for the development of an ADI. Therefore, using an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for intrahuman variability and 10 to extrapolate from subchronic to chronic expsoure) an ADI of 0.316 mg/kg/day or 22.1 mg/day for a 70 kg man can be derived.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The studies (Gibel et al., 1974, 1975; Hillbom et al., 1974a,b; Toxicity Research Laboratory, 1986) have addressed the issue of the repeated oral exposure of experimental animals to isobutanol. These studies were discussed in Section 5.5. and are summarized in Table 9-1.

As seen from Table 9-1, the most severe effect was increased mortality of rats, which warrants an RV_e of 10. This effect was observed at the lowest transformed dose tested. Because the effects on the gastrointestinal mucosa and liver of rats in the studies by Hillbom et al. (1974a,b) and Toxicity Research Laboratory (1986) warrant a lower RV_e and the transformed doses, even if divided by an uncertainty factor of 10 to approximate chronic exposure, are higher than 45.7 mg/kg/day, it is not necessary to calculate CSs for the Hillbom et al. (1974a,b) or Toxicity Research Laboratory (1986) studies.

The data used to calculate the CS and RQ for isobutanol are presented in Tables 9-2 and 9-3. Multiplying the animal dose of 45.7 mg/kg/day by the cube root of the ratio of the reference rat body weight (0.35 kg) to the reference human body weight (70 kg) and by 70 kg results in a MED of 547 mg/day, which corresponds to an RV_d of 1.4. Multiplying the RV_d by the RV_e of 10 results in a CS of 14, which corresponds to an RQ of 1000.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

In the only study of the carcinogenicity of isobutanol, Gibel et al. (1974, 1975) treated a group of 19 Wistar rats by gavage with isobutanol at 0.2 mℓ/kg (160 mg/kg) 2 days/week from 70 days of age until death. Another group of 24 rats were treated subcutaneously with 0.05 mℓ/kg 2 days/week. Controls were treated orally or subcutaneously with physiological saline. The mean survival times of the rats treated by gavage and by

TABLE 9-1

Toxicity Summary for Isobutanol in Wistar Rats[a]

Sex	No. at Start	Average Weight (kg)[b]	Vehicle/ Physical State	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
M	5	0.35	drinking water	2 M solution for 2 months	20,754[c]	Decreased relative liver weight; decreased content of fat, glycogen and RNA in liver; small hepatocytes, Mallory's alcoholic hyaline bodies; gastric and intestinal bleeding; enlarged and gas- or food-filled stomachs	Hillbom et al., 1974a
M	6	0.35	drinking water	1 M solution for 4-6 months	7,412[d]	Small-intestinal bleeding, enlarged and gas- or food-filled stomachs	Hillbom et al., 1974a,b
NR	19 treated 25 controls	0.35	isobutanol liquid by gavage; controls received saline	0.2 mL/kg, 2 days/week for lifespan	45.7[e]	Increased mortality; a variety of non-neoplastic lesions including necrosis and fatty degeneration of the liver, cirrhosis and hepatitis	Gibel et al., 1974, 1975
M,F	30 each	0.35	isobutanol liquid by gavage	0, 100, 316, 1000 mg/kg/day for 13 weeks	1,000	Slight reduction in body weight. Ataxia and hypoactivity	Toxicity Research Laboratory, 1986

[a]Purity was not reported

[b]Assumed

[c]Isobutanol consumption data not provided. 2 M isobutanol = 148.24 g/L. Assuming that a 0.35 kg rat consumes 0.049 L/day (Durkin, 1985) the transformed dose is 7264 mg/day or 20,754 mg/kg/day

[d]Calculated from isobutanol consumption data provided by Hillbom et al. (1974a)

[e]Calculated by multiplying 0.2 mL/kg by the density of isobutanol (0.798 g/mL) to yield 0.1596 g/kg or 160 mg/kg; multiplying by 2 days/7 days yields 45.7 mg/kg/day

NR = Not reported

TABLE 9-2

Oral Composite Scores for Isobutanol in Wistar Rats*

Animal Dose (mg/kg/day)	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
45.7	547	1.4	Increased mortality	10	14	1000

*Source: Gibel et al., 1974, 1975

TABLE 9-3

Isobutanol

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral (gavage)
Dose*:	547 mg/day
Effect:	increased mortality
Reference:	Gibel et al., 1974, 1975
RV_d:	1.4
RV_e:	10
Composite Score:	14
RQ:	1000

*Equivalent human dose

subcutaneous injection were 495 and 544 days, respectively, while mean survival of controls was >643 days. There was a statistically significant increased incidence of total benign tumors in orally treated rats compared with controls, but the incidence of malignant tumors was not significantly different from control (see Table 5-1). The incidence of benign tumors in the subcutaneously treated rats was 3/24 compared with 0/25 in controls (p=0.11), while the incidence of malignant tumors in the subcutaneously treated rats was 8/24 compared with 2/25 in controls (p=0.03). The eight malignancies in the rats treated subcutaneously were two forestomach carcinomas, two hepatic sarcomas, two retroperitoneal sarcomas, a splenic carcinoma and a mesothelioma.

No significant increased incidence of any type of tumor at any site occurred in the rats treated orally or subcutaneously. Therefore, according to the U.S. EPA (1984) Proposed Guidelines for Cancer Risk Assessment and IARC, the animal data are inadequate to assess the carcinogenicity of isobutanol; the calculation of an F factor is not warranted. No data regarding the carcinogenicity of isobutanol to humans were available. Thus isobutanol is most appropriately classified as an IARC Group 3 chemical. Based on U.S. EPA (1984) guidelines for carcinogen risk assessment, the overall weight of evidence classification is Group D, meaning isobutanol cannot be classified as a human carcinogen, and under the hazard ranking scheme, no direct ranking is possible for isobutanol.

ISOBUTANOL

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. Cincinnati, OH. p. 235.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment Adopted by ACGIH with Intended Changes for 1985-1986. Cincinnati, OH. p. 11, 21 and 38.

Anbar, M. and P. Neta. 1967. A compilation of specific bimolecular rate constants for the reactions of hydrated electrons, hydrogen atoms and hydroxyl radical with inorganic and organic compounds in aqueous solution. Int. J. Appl. Radiat. Isotopes. 18: 493-523.

Atkinson, R. 1985. Kinetics and mechanisms of the gas phase reactions of the hydroxyl radical with organic compounds under atmospheric conditions. Prepublication copy submitted to Chem. Rev.

Bonte, W., E. Ruedell, R. Sprung, et al. 1981. Experimental studies on detection of small doses of higher aliphatic alcohols in human blood. Blutalkohol. 18: 399-411. (CA 9[illegible]4036f)

Botta, D., P.L. Castellani and E. Mantica. 19[illegible]. Groundwater pollution by organic solvents and their microbial degradation products. Comm. Eur. Commun. EUR 8518: 261-275.

Bridie, A.L., C.J.M. Wolff and M. Winter. 1979a. BOD and COD of some petrochemicals. Water Res. 13: 627-630.

Bridie, A.L., C.J.M. Wolff and M. Winter. 1979b. The acute toxicity of some petrochemicals to goldfish. Water Res. 13(7): 623-626.

Bringmann, G. 1978. Determination of the biological toxicity of waterbound substances towards protozoa. I. Bacteriovorous flagellates (model organism: Entosiphon sulcatum Stein). Z. Wasser Abwasser Forsch. 11(6): 210-215.

Bringmann, G. and R. Kuehn. 1977a. Results of the damaging effect of water pollutants on Daphnia magna. Z. Wasser Abwasser Forsch. 10: 161-166.

Bringmann, G. and R. Kuehn. 1977b. Limiting values for the damaging action of water pollutants to bacteria (Pseudomonas putida) and green algae (Scenedesmus quadricauda) in the cell multiplication inhibition test. Z. Wasser Abwasser Forsch. 10: 87-98.

Bringmann, G. and R. Kuehn. 1978. Testing of substances for their toxicity threshold: Model organisms Microcystis (Diplocystis) aeruginosa and Scenedesmus quadricauda. Exp. Use Algal Cult. Limnol. p. 275-284.

Bringmann, G. and R. Kuehn. 1982. Results of toxic action of water pollutants on Daphnia magna Straus tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1): 1-6.

Browning, E. 1965. Toxicity and Metabolism of Industrial Solvents. Elsevier, Amsterdam.

Burrows, W.D. and R.S. Rowe. 1975. Ether soluble constituents of landfill leachate. J. Water Pollut. Control Fed. 47(5): 921-923.

Carter, R.V. and B. Linsky. 1974. Gaseous emissions from whiskey fermentation units. Atmos. Environ. 8(1): 57-62.

CFR (Code of Federal Regulations). 1985. OSHA (Occupational Safety and Health Administration). Safety and Health Standards. 29 CFR 1910. 1000.

Chang, T., J. Lewis and A.J. Glazko. 1967. Effect of ethanol and other alcohols on the transport of amino acids and glucose by everted sacs of rat small intestine. Biochim. Biophys. Acta. 135: 1000-1007.

Clegg, D.J. 1964. The hen egg in toxicity and teratogenicity studies. Food Cosmet. Toxicol. 2: 717-727. (Cited in U.S. EPA, 1983; TSCA-ITC, 1980)

Curtis, C., A. Lima, S.J. Lozano and G.D. Veith. 1982. Evaluation of a bacterial bioluminescence bioassay as a method for predicting acute toxicity of organic chemicals to fish. ASTM Spec. Tech. Publ. 766: 170-178.

David, E.T., I. Fischer and K. Moldave. 1983. Studies on the effect of ethanol on eukaryotic protein synthesis in vitro. J. Biol. Chem. 258: 7702-7706.

DeCeaurriz, J.C., J.C. Micillino, P. Bonnet and J.P. Guenier. 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett. 9(2): 137-144.

Dias, F.F. and M. Alexander. 1971. Effect of chemical structure on the biodegradability of aliphatic acids and alcohols. Appl. Microbiol. 22: 1114-1118.

Dilling, W.L., C.J. Bredeweg and N.B. Tefertiller. 1976. Organic photochemistry. XIII. Simulated atmospheric photodecomposition rates of methylene chloride, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and other compounds. Environ. Sci. Technol. 10: 351-356.

Dorfman, L.M. and G.E. Adams. 1973. Reactivity of the hydroxyl radical in aqueous solution. National Bureau of Standards, Washington, DC. 51 p.

Durkin, P. 1985. Reference Values for Risk Assessment. Prepared by Syracuse Research Corp, Syracuse, NY, under Contract No. 68-03-3228. ECAO, U.S. EPA, Cincinnati, OH.

Farley, F.F. 1977. Photochemical reactivity classification of hydrocarbons and other organic compounds. Int. Conf. on Photochemical Oxidant Pollution and Its Control. EPA-600/3-77-001B. p. 713-727.

Gaillard, D. and R. Derache. 1966. Effect of some aliphatic alcohols on the mobilization of various lipid fractions in the rat. Food Cosmet. Toxicol. 4: 515-520. (Fre.)

Gerhold, R.M. and G.W. Malaney. 1966. Structural determinants in the oxidation of aliphatic compounds by activated sludge. J. Water Pollut. Control Fed. 38: 562-579.

Gibel, W., K. Lohs, G.P. Wildner and T. Schramm. 1974. Experimental studies on the cancerogenic effect of higher alcohols, as illustrated by 3-methyl-1-butanol, 1-propanol, and 2-methyl-1-propanol. Z. Exp. Chir. Chir. Forsch. 7(4): 235-239. (Ger.)

Gibel, W., K. Lohs and G.P. Wildner. 1975. Carcinogenic activity of propanol, 2-methyl-1-propanol, and 3-methyl-1-butanol. Arch. Geschwulstforsch. 45(1): 19-24. (Ger.)

Gilgan, M.W. and B.G. Burns. 1976. The anesthesia of the lobster (Homarus americanus) by isobutanol injection. Can. J. Zool. 54: 1231-1234.

Graedel, T.E. 1978. Chemical Compounds in the Atmosphere. Academic Press, New York, NY.

Guesten, H., W.G. Filby and S. Schoof. 1981. Prediction of hydroxyl radical reaction rates with organic compounds in the gas phase. Atmos. Environ. 15: 1763-1765.

Hammerton, C. 1955. Observations on the decay of synthetic anionic detergents in natural water. J. Appl. Chem. 5: 517-524.

Hangartner, M. 1979. Sampling and analysis of odorous compounds in waste water treatment plants. Int. J. Environ. Anal. Chem. 6(2): 161-169.

Hansch, C. and A.J. Leo. 1981. Medchem. Project. Issue No. 19. Pomona College, Claremont, CA.

Hatfield, R. 1957. Biological oxidation of some organic compounds. Ind. Eng. Chem. 49: 192-196.

Hawley, G.G. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Company, Inc., New York. p. 576.

Hedlund, S.G. and K.H. Kiessling. 1969. Physiological mechanism involved in hangover. I. Oxidation of some lower aliphatic fusel alcohols and aldehydes in rat liver and their effect on the mitochondrial oxidation of various substrates. Acta Pharmacol. Toxicol. 27: 381-396.

Hermens, J., E. Broekhuyzen, H. Canton and R. Wegman. 1985. Quantitative structure activity relationships and mixture toxicity studies of alcohols and chlorohydrocarbons: Effects on growth of Daphnia magna. Aquat. Toxicol. 6(3): 209-217.

Heukelekian, H. and M.C. Rand. 1955. Biochemical oxygen demand of pure organic compounds. J. Water Pollut. Control Assoc. 29: 1040-1053.

Hillbom, M.E., K. Franssila and O.A. Forsander. 1974a. Effects of chronic ingestion of some lower aliphatic alcohols in rats. Arukoru Kenkyu. 9(2): 101-108.

Hillbom, M.E., K. Franssila and O.A. Forsander. 1974b. Effects of chronic ingestion of some lower aliphatic alcohols in rats. Res. Commun. Chem. Pathol. Pharmacol. 9(1): 177-180.

Hilscher, H., E. Geissler, K. Lohs and W. Gibel. 1969. Toxicity and mutagenicity of single fusel oil components on Escherichia coli. Acta Biol. Med. Ger. 23(6): 843-852. (Ger.)

Hine, J. and P.K. Mookerjee. 1975. The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. J. Org. Chem. 40(3): 292-298.

Howe, R.B. and K.S. Crump. 1982. GLOBAL82. A Computer Program to Extrapolate Quantol Animal Toxicity Data to Low Doses. Prepared for Office of Carcinogen Standards, OSHA, U.S. Dept. of Labor under Contract No. 41USC252C3.

Hwang, T.K., S.M. Ong, C.C. Seow and H.K. Tan. 1978. Chemical composition of palm oil mill effluents. Planter. 54: 749-756. (CA 91:128487k)

Juhnke, I. and D. Luedemann. 1978. Results of the study of 200 chemical compounds on acute fish toxicity using the Golden Orfe test. Z. Wasser Abwasser Forsch. 11(5): 161-164.

Kamil, J.A., J.N. Smith and R.T. Williams. 1953. Studies in detoxication. 46. The metabolism of aliphatic alcohols. The glucuronic acid conjugation of acyelic aliphatic alcohols. Biochem J. 53: 129-136.

Kawasaki, M. 1980. Experiences with the test scheme under the chemical control law of Japan: An approach to structure-activity correlations. Ecotoxicol. Environ. Safety. 4: 444-454.

Kondakova, L.V., M.A. Lebedev, M.I. Stepanova, Y.K. Shaposhnikov and N.N. Kirillova. 1982. Composition of waste gases escaping from vacuum systems in the production of synthetic aromatic principles. Prom. Sanit. Ochistka. Gazov. 6: 19-20. (CA 98:1128934)

Kushneva, V.S., G.A. Koloskova, I.G. Koltunova and V.T. Kirilenko. 1983. Experimental data on hygienic regulations for isobutyl alcohol in the air of the working environment. Gig. Tr. Prof. Zabol. (1): 46-7. (Russ.) (CA 98:120807p)

Langley, W.D. 1970. Intermediate products in the bacterial decomposition of hexadecanol and octadecanol. TR-29. Texas A&M Univ. Water Resources Inst. College Station, TX.

Lawler, G.M., Ed. 1977. Chemical Origins and Markets, 5th ed. Stanford Research Institute, Menlo Park, CA. p. 98.

Lester, D. and G.D. Benson. 1970. Alcohol oxidation in rats inhibited by pyrazole, oxines and amides. Science. 169: 282-284.

Linden, E., B.E. Bengtsson, O. Svanberg and G. Sundstrom. 1979. The acute toxicity of 78 chemicals and pesticide formulations against two brackish water organisms, the bleak (Alburnus alburnus) and the harpacticoid (Nitocra spinipes). Chemosphere. 8: 843-845.

Luedersdorf, R., G. Schaecke and A. Fuchs. 1985. Organic solvents and their key components. Staub - Reinhalt. Luft. 45(2): 88-89. (CA 103:10701p)

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. McGraw-Hill Book Co., New York. p. 4-9, 7-4, 15-16.

Mackay, D. and A.T.K. Yeun. 1983. Mass transfer coefficient correlations for volatilization of organic solutes from water. Environ. Sci. Technol. 17: 211-217.

Maickel, R.P. and D.P. McFadden. 1979. Acute toxicity of butyl nitrites and butyl alcohols. Res. Commun. Chem. Pathol. Pharmacol. 26(1): 75-83.

McComb, J.A. and D.B. Goldstein. 1975. The dose response effects of short chain alcohols administered to mice intraperitoneally. Pharmacologist. 17(2): 198.

McCreery, M.J. and W.A. Hunt. 1978. Physicochemical correlates of alcohol intoxication. Neuropharmacology. 17: 451-461.

McKinney, R.E. and J.S. Jeris. 1955. Metabolism of low molecular weight alcohols by activated sludge. Sewage Ind. Wastes. 27: 728-735.

Mill, T., D.G. Hendry and H. Richardson. 1980. Free-radical oxidants in natural water. Science. 207: 886-887.

Munch, J.C. 1972. Aliphatic alcohols and alkyl esters: Narcotic and lethal potencies to tadpoles and to rabbits. Ind. Med. Surg. 41(4): 31-33.

Price, K.S., G.T. Waggy and R.A. Conway. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollut. Control Fed. 46: 63-77.

Roach, M.K., D.L. Davis, W. Pennington and E. Nordyke. 1973. Effect of ethanol on the uptake by rat brain synaptosomes of tritium-labeled DL-norepinephrine, tritium-labeled 5-hydroxytryptamine, tritium-labeled GABA, and tritium-labeled glutamate. Life Sci. 12: 433-441.

Rogawski, M.A., S. Knapp and A.J. Mandell. 1974. Effects of ETOH on TRP Q4-ase activity from striate synaptosomes. Biochem. Pharmacol. 23: 1955-1962.

Rowe, V.K. and S.B. McCollister. 1982. In: Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. IIC. John Wiley and Sons, Inc., New York. p. 4578-4582.

Rumsby, M.G. and J.B. Finean. 1966. The action of organic solvents on the myelin sheath of peripheral nerve tissue. II. Short-chain aliphatic alcohols. J. Neurochem. 13: 1509-1511.

Sabljic, A. 1984. Prediction of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32: 243-246.

Saito, M. 1975. Metabolism of lower alcohols. Nichidai Igaku Zasshi. 34: 569-585. (Cited in TSCA-ITC, 1980; U.S. EPA, 1983)

Sasaki, S. 1978. The scientific aspects of the chemical substance control law in Japan. In: Aquatic Pollutants: Transformation and Biological Effects, O. Hutzinger, L.H. Von Letyoeld and B.C.J. Zoeteman, Ed. Pergamon Press, Oxford. p. 283-298.

Seitz, B. 1972. Severe vertigo following handling of butanol and isobutanol: Three cases. Arch. Mal. Prof. Med. Trav. Secur. Soc. 33: 393-395. (Fre.) (Cited in U.S. EPA, 1983; TSCA-ITC, 1980)

Sherman, P.D. 1978. Butyl alcohols. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 4, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 342-344.

Shoemaker, W.J. 1981. The neurotoxicity of alcohols. Neurobehav. Toxicol. Teratol. 3(4): 431-436.

Smyth, H.F., C.P. Carpenter, C.S. Weil and V.C. Pozzani. 1954. Range-finding toxicity data: List V. Arch. Ind. Hyg. Occup. Med. 10: 61.

SRC (Syracuse Research Corporation). 1980. Isobutyl Alcohol Hazard Profile. Prepared by Center for Chemical Hazard Assessment, Syracuse Research Corporation Syracuse, NY. ECAO, U.S. EPA, Cincinnati, OH.

SRI (Stanford Research Institute). 1985. 1985 Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA.

Swann, R.L., D.A. Laskowski, P.J. McCall, K. Vander Kuy and H.J. Dishburger. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Res. Rev. 85: 17-28.

Tang, J., Q.Z. Jin, G.H. Shen, C.T. Ho and S.S. Chang. 1983. Isolation and identification of volatile compounds from fried chicken. J. Agric. Food Chem. 31: 1287-1292.

Toxicity Research Laboratory. 1986. Rat oral subchronic toxicity study with isobutyl alcohol. Sponsored by U.S. EPA, Office of Solid Waste, Washington, DC. (Unpublished)

TSCA-ITC. 1980. Hazard Information Review: Isobutanol Prep. for TSCA Interagency Testing Committee Prep. by Enviro Control, Inc., Rockville, MD 20852. IR-212, October 31, 1980.

U.S. EPA. 1977. Computer print-out of nonconfidential production data from TSCA inventory. OPTS, CID, U.S. EPA, Washington, DC.

U.S. EPA. 1979. Acceptable Common Names and Chemical Names for the Ingredient Statement on Pesticide Labels, 4th ed. U.S. EPA, Office of Pesticide Programs, Hazard Evaluation Division, Residue Chemistry Branch, Washington, DC. EPA-540/9-77-017.

U.S. EPA. 1983. CHIP (Chemical Hazard Information Profile) - Isobutyl Alcohol. Prepared by Dynamac Corp., Rockville, MD, under Contract No. 68-01-6239. U.S. EPA, OTS, Cincinnati, OH.

U.S. EPA. 1984. Proposed Guidelines for Carcinogen Risk Assessment; Request for Comments. Federal Register. 49(227): 46294-46301.

USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S. Production and Sales, 1984. USITC Publ. 1985, Washington, DC. p. 256.

Veith, G.D. 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. ASTM STP 707: 116-129.

Veith, G.D., D.J. Call and L.T. Brooke. 1983. Structure-toxicity relationships for the fathead minnow, Pimephales promelas: Narcotic industrial chemicals. Can. J. Fish. Aquat. Sci. 40(6): 743-748.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold Company, New York, NY. p. 765-766.

Weese, H. 1928. Vergleichende Untersuchungen uker die wirksamkeit und giffigkeit der dampfe niederer aliphatischer alkohole. Arch Exp. Pathol. Pharmakol. 135: 118. (Cited in Browning, 1965; Wimer et al., 1983)

Windholz, M. 1983. The Merck Index. An Encyclopedia of Chemicals, Drugs and Biologicals, 10th ed. Merck and Co., Inc., Rahway, NJ. p. 4984.

Yasuhara, A, H. Shiraishi, M. Tsuji and T. Okuno. 1981. Analysis of organic substance in highly polluted water by mass spectrometry. Environ. Sci. Technol. 15: 570-573.

Yasuhara, A., K. Fuwa and M. Jimbu. 1984. Identification of odorous compounds in fresh and rotten swine manure. Agric. Biol. Chem. 48: 3001-3010.

Yonezsuwa, Y. and Y. Urushigawa. 1979. Chemico-biological interactions in biological purification systems. V. Relation between biodegradation rate constants of aliphabic alcohols by activated sludge and their partition coefficient in a 1-octanol water system. Chemosphere. 8: 139-142.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. p. 2878.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.